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A rare case report of a diagnostic dilemma: Cervical leiomyosarcoma versus Extraintestinal Gastrointestinal Stromal Tumor

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ABSTRACT

Aim: The aim of this study is to report a rare case that posed a diagnostic dilemma between cervical leiomyosarcoma (LMS) & extraintestinal gastrointestinal sarcoma (GIST). *Methodology:* A 47 years old postmenopausal female with a history of whitish foul-smelling vaginal discharge for three months presented to our department. Per vaginal & per speculum examination showed a massive exophytic cervical growth. On cervical biopsy, it was suggestive of leiomyosarcoma. Positron emission tomography-computed tomography (PET-CT) scan did not reveal any visceral metastasis. She underwent nerve sparing modified radical hysterectomy. The retrieved specimen was sent for final histopathological evaluation (HPE) and immunohistochemical staining (IHC). This was followed by mutational analysis of the specimen. *Conclusions:* This study has shown a CD117 & CD34 immunoreactive sarcoma masquerading as an extraintestinal GIST. CD117 is not specific for GIST. The use of biomarkers and molecular testing is indispensable for a thorough evaluation. Surgery is the primary modality of treatment. Following surgery, the patient has undergone adjuvant chemotherapy. There was no evidence of tumor recurrence after 12 months of follow up.

Keywords: Cervix, sarcoma, immunohistochemistry, cd117, mutational analysis

1. INTRODUCTION

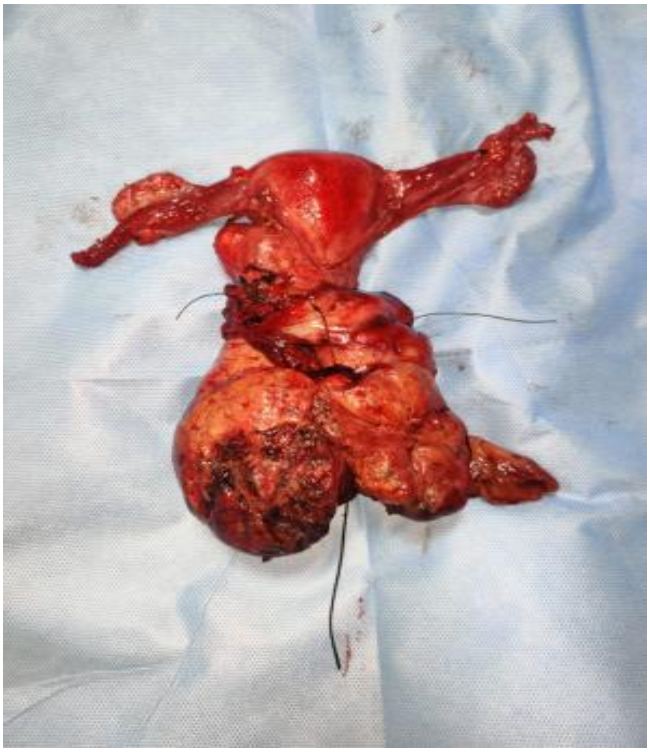
Primary sarcoma involving the cervix are rare, affecting approximately one percent. And the incidence of cervical leiomyosarcoma is 0.21%. The majority of patients present with vaginal bleeding and a cervical mass at diagnosis. They generally occur in fourth to sixth-decade females. Histopathological diagnosis of

leiomyosarcoma (LMS), is confirmed by immunohistochemical (IHC) stains. Smooth muscle markers like desmin, smooth-muscle actin (SMA), h-caldesmon, are positive in LMS. CD 117 is not specific for gastrointestinal stromal tumors (GIST), as other mesenchymal tumors, such as non-GIST spindle cell neoplasms like LMS, rhabdomyosarcoma, synovial sarcoma, dermatofibrosarcoma protuberans (DFSP), also show CD 117 positivity. So, CD 117 (KIT protein) positivity by IHC is unreliable. Hence mutational diagnosis is done for final confirmation. We present a rare case of cervical LMS with diagnostic dilemma that was resolved by negative mutational analysis for c-KIT and PDGFRA. This case was managed using a combination of treatment modalities.

2. METHODS

A 47 years old postmenopausal female with a history of whitish foul-smelling vaginal discharge for three months presented to our department. Pelvic examination showed a massive exophytic cervical growth. Hematological and routine blood chemistry parameters were within reference ranges. Chest radiography showed clear lung and pleural fields. Ultrasound of the abdomen and pelvic region revealed a hypoechoic cervical lesion. On cervical biopsy, it was suggestive of leiomyosarcoma. PET-CT showed FDG avid large heterogenously enhancing cervical lesion measuring 89x83x77 mm (max SUV 69.2).

The lesion was indenting posterior wall of urinary bladder and there was suspicious loss of fat plane with rectum. Tiny bilateral external iliac lymph nodes were noted, with no FDG uptake. And no metabolically active skeletal or visceral lesions were seen. The cystoscopy and sigmoidoscopy examinations revealed no abnormalities. So, clinical stage for this case, was cT2N0M0 Gx (Stage IB FIGO). She underwent nerve sparing modified radical hysterectomy procedure. Intraoperative examination revealed a massive foul-smelling mass originating from cervix (12x8 cms). Intraoperative cystoscopy and methylene blue dye test did not reveal any bladder or ureteral injuries. Air leak test was negative.



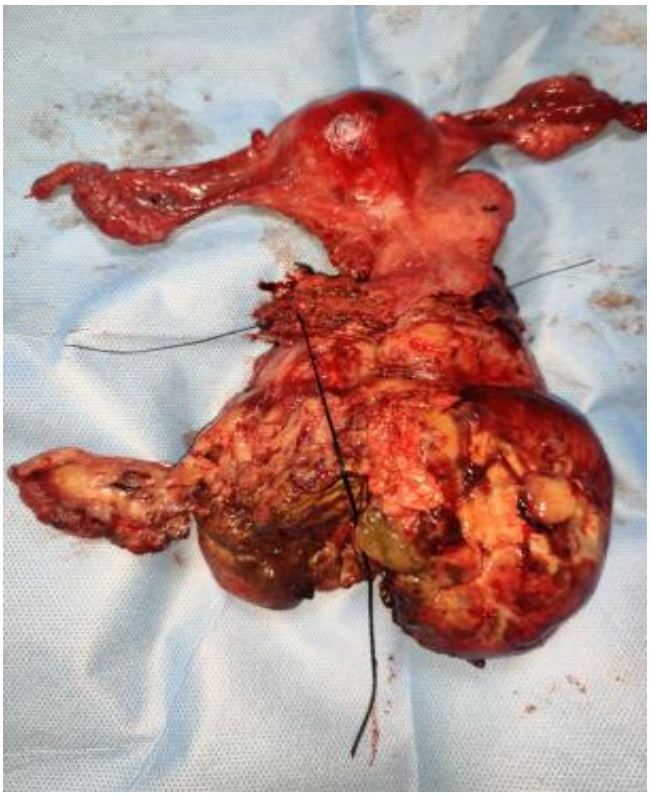


Figure 1 Cervical lesion, anterior and posterior view respectively

Final histopathological examination of surgical specimen revealed a pendunculated mass (9x9x6.5 cms) arising from anterior lip of cervix. Microscopically, the tumor was composed of spindle cells arranged in fascicles and bundles. The tumor cells had elongated, blunt ended nuclei with moderate amount of eosinophilic fibrillary cytoplasm. Moderate nuclear pleomorphism was observed. These findings were consistent with a diagnosis of leiomyosarcoma. All surgical margins were free of tumor. There was no evidence of lymphovascular invasion, and the parametrium was free of tumor involvement. The tumor was staged as pT1b (FIGO IB). The tumor cells stained positive for SMA, CD34, CD 117, hCaldesmon. S100, CD10, pankeratin, ER, PR, MSA, ALK, DOG1, CD31, myoD1 and myogenin stains were negative. SDH-B was retained. Mitosis was 12-13/50 high power field. And ki-67 was 35%. IHC analysis of biopsy specimen revealed a profile consistent with extraintestinal GIST (spindle cell type).

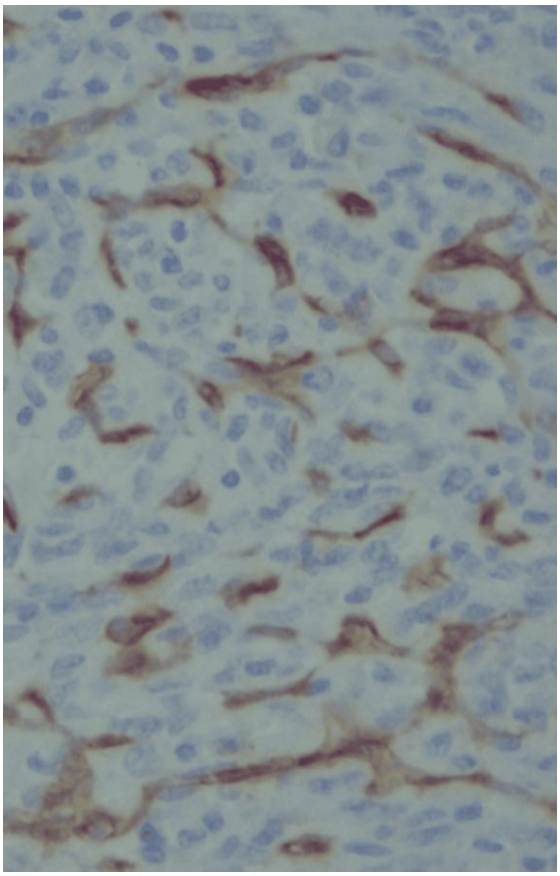


Figure 2 CD 117 immuno-staining in tumoral cells (Magnification 40x)

Final histopathology and IHC had put us in a dilemma between LMS & extraintestinal GIST. Mutational analysis for mutations in PDGFRA & cKIT genes was negative, supporting the diagnosis of leiomyosarcoma. After initial surgery patient was followed up regularly by local examination, pelvic examination and ultrasonography of abdomen and pelvic region. A post-hysterectomy status was noted. A multidisciplinary oncology team recommended a treatment regimen of adjuvant chemotherapy followed by adjuvant radiotherapy. Adjuvant chemotherapy was started four weeks after surgery.

Patient received four cycles of three weekly intravenous gemcitabine and docetaxel regimen. As per her BSA of 1.59 square meters, 1070 mg (675mg/m2) of gemcitabine (day one and eight) and 120 mg (75mg/m2) of docetaxel (day eight) were given, which was well-tolerated by the patient. Patient defaulted for adjuvant radiotherapy (external beam radical radiotherapy and vaginal cuff high dose rate brachytherapy).

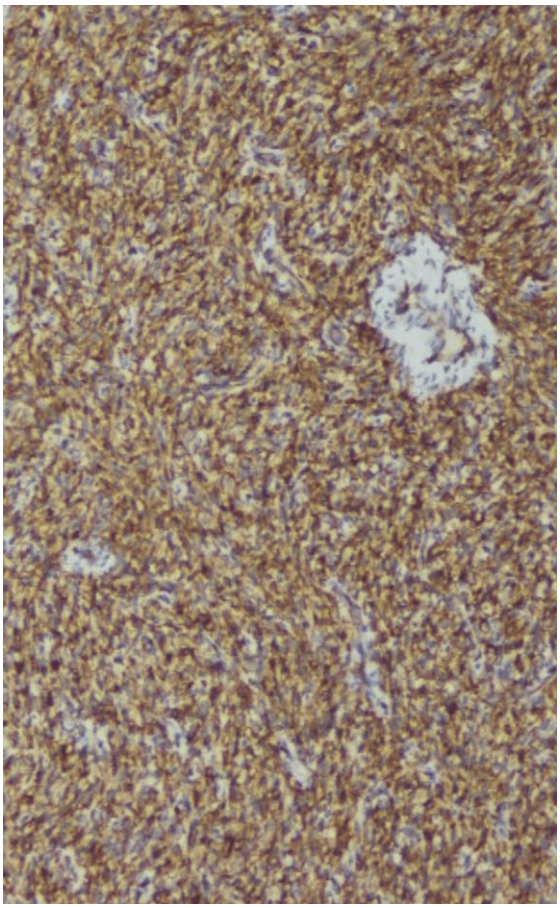


Figure 3 CD 34 immuno-staining in tumoral cells (Magnification 40x)

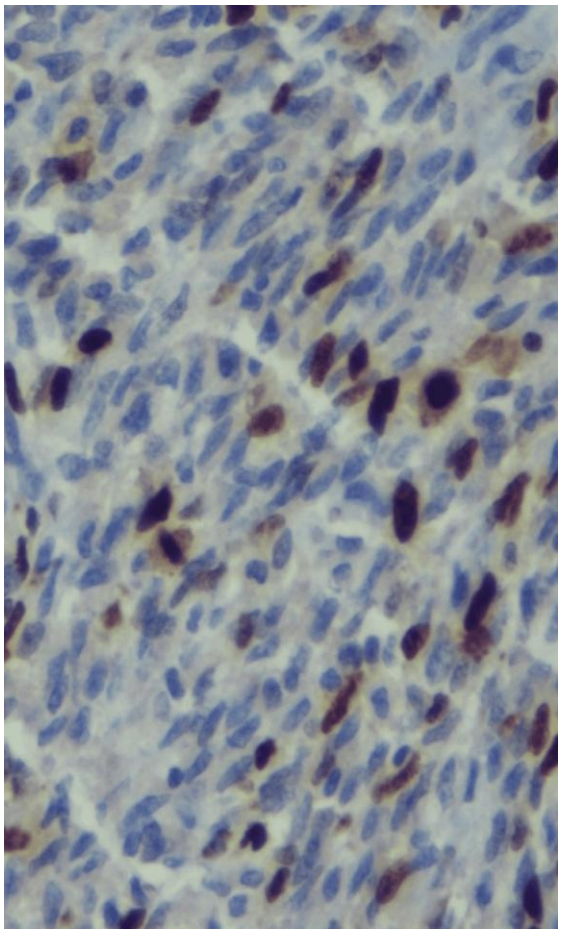


Figure 4 Ki67 immuno-staining in tumoral cells (Magnification 40x)

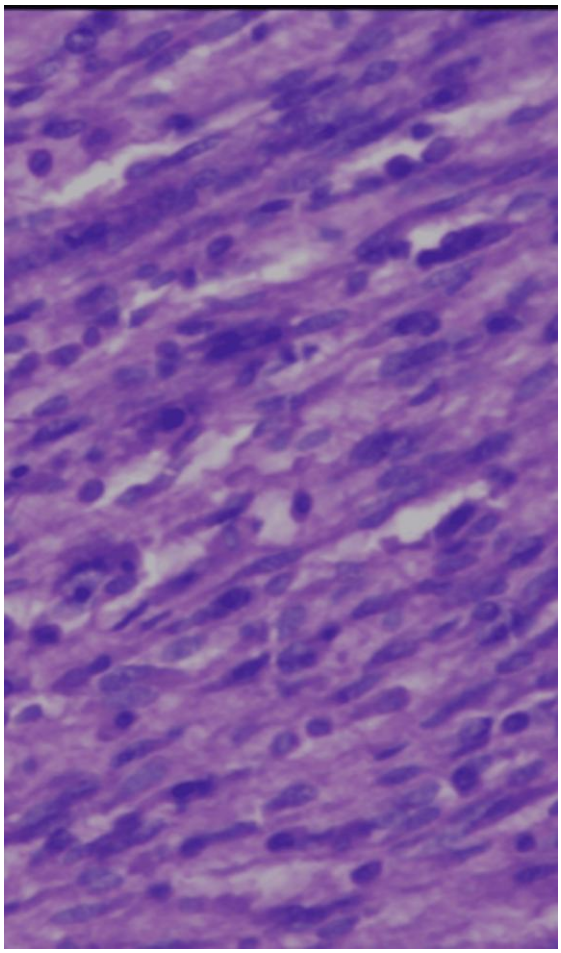


Figure 5 Hematoxylin and Eosin staining in tumoral cells (Magnification 40x). The given slide image shows bland spindle cells with faintly eosinophilic cytoplasm in syncytial pattern.

3. RESULTS

She was scheduled for follow-up visits on a quarterly basis with local examination, pelvic examination and ultrasound of abdomen and pelvic region. An annual contrast-enhanced magnetic resonant scan of the abdomen and pelvis was also recommended. Despite defaulting on radiotherapy, our case had a favourable outcome with a good locoregional response. She was asymptomatic without any evidence of tumor recurrence after 12 months of follow-up.

4. DISCUSSION

Leiomyosarcomas are malignant tumors of cells showing smooth muscle features. Most available data on cervical leiomyosarcomas comes from case reports and small case series. They generally affect the perimenopausal and postmenopausal populations, with complaints of vaginal bleeding and bulky cervical mass. Cervical biopsy is the first step for assessment of any suspicious cervical mass. LMS is usually identifiable on light microscopy. IHC stains are used for confirmation in suspicious LMS or in highly undifferentiated tumors. IHC stains are positive for smooth-muscle origin markers like desmin, smooth-muscle actin and h-caldesmon. Compared to leiomyoma, LMS has lower expression of estrogen (40% in LMS versus 70% in leiomyoma) and progesterone receptors (Leitao et al., 2004).

The expression of CD117 (KIT mutation) is seen consistently amongst LMS, but this does not translate into oncogenic mutation. Hence, drugs targeting KIT mutation (Imatinib) are not practical here. There have also been reports of dilemma between LMS and GIST due to CD117 (c-KIT) positivity, which was confirmed by mutational analysis (Riddle et al., 2011). KIT protein positivity established by IHC may be unreliable in some instances because of some KIT-negative GISTs and KIT-positive non-GIST spindle cell neoplasms.

Antigen retrieval may be the cause for this spurious positivity. Demonstrating c-KIT and PDGFRA mutations are more reliable than IHC, for diagnosing GISTs (Riddle et al., 2011). One study has reported that patients with low expression of Ki-67, p53, p16, and Twist and high expression of bcl-2, had longer recurrence-free survival (D'Angelo et al., 2009).

For LMS confined to the cervix, the optimal management is generally surgical management. The type of hysterectomy doesn't affect oncological outcome if surgical margins are free. While debatable, lymphadenectomy is often omitted due to low incidence of lymph nodes metastasis. Combined modality treatment can significantly prolong overall survival (Khosla et al., 2012). Tumor size, stage, grade, mitotic count, age and menopausal status are prognostic factors. Advanced stage, older age (>51years), postmenopausal status and larger tumor size (>5 cms), are significantly associated with poorer survival in cervical LMS (Giuntoli et al., 2003).

A clinical nomogram has been developed by Memorial Sloan Kettering using age, grade, tumor size, mitotic rate, presence of cervical invasion, locoregional metastasis, and distant metastasis; to predict 5-year overall survival (Zivanovic et al., 2012). Adjuvant pelvic irradiation improves locoregional control in uterine LMS (Larson et al., 1990; Gadducci et al., 1996; Major et al., 1993). There is no statistically significant association between the administration of adjuvant pelvic irradiation and improved survival. Chemotherapeutic agents for uterine LMS are not standardized, but combinations containing doxorubicin are commonly used (Giuntoli et al., 2003; Bansal et al., 2010). A frequently employed treatment regimen for advanced or metastatic forms involves doxorubicin and isofosfamide notwithstanding its considerable toxicity profile.

Other chemotherapy drugs, such as cyclophosphamide, gemcitabine and docetaxel, have been used with a response rate of approximately 30% (Sutton et al., 1996). A combined modality of treatment is preferred for cervical LMS. Our findings are consistent with (Riddle et al., 2011). Our approach to treating the tumor was similar to that of most other studies, including the administration of adjuvant chemotherapy to our patient (Dhull et al., 2013; Lebbe et al., 2023). Our study also included a lesion on the anterior lip of cervix, which correlates with the findings of Dhull et al., (2013). While the efficacy of adjuvant chemotherapy for LMS is uncertain, it may be considered for advanced, metastatic, unresectable or recurrent disease (Hensley et al., 2018; Sutton et al., 1996).

Overall, cervical has a poor prognosis. The 5-year survival rate for stage IA, IB, II and III is 80%, 67%, 42% and 20% respectively (Fadare, 2006; Bansal et al., 2010). In a follow-up study spanning six to eight months, Dhull et al., (2013) and Bhatia et al., (2015) found no recurrence. This is a finding consistent with our own observations. The prognosis of cervical LMS is inferior compared to its common counterparts, like squamous cell carcinoma and adenocarcinoma. She was scheduled for follow-up visits on a quarterly basis for first two years.

5. CONCLUSION

Cervical LMS is a rare pathology with quite aggressive recurrence and metastasis. Diagnosing uterine LMS can be challenging due to its similar IHC profile to other CD177-positive sarcomas. Biomarkers and molecular testing are essential for accurate diagnosis. Surgery is the primary treatment modality for localised cervical LMS. The effectiveness of chemotherapy and radiotherapy is debatable, as no large series has been conducted till date. Regular follow-up and further research into combined therapies are needed.

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Authors contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.
Concept and design: BB, VKKV, NYS, VK
Acquisition, analysis or interpretation of data: BB, VKKV, NYS, VK
Drafting of the manuscript: BB, VK
Critical review of the manuscript for important intellectual content: BB, VKKV, NYS, VK
Supervision: BB, VKKV, NYS, VK

Informed consent

Written & Oral informed consent was obtained from the participant included in the study.

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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